

REMARKS

Claims 31-35, 40-42, 51, 58-62, 67-69, 78, 97 and 98 were pending.

Claims 31, 41, 42, 58, 68, 69 have been amended. Claims 32-35, 40, 51, 59-62, 67, 78, 97 and 98 have been previously resented. Claim 99 has been added. Upon entry of these amendments, claims 31-35, 40-42, 51, 58-62, 67-69, 78 and 97-99 are pending and under consideration.

I. CLAIMS AMENDMENTS

Claims 31 and 58 have been amended for clarity. Support for these amendments can be found, for example, on page 6, line 28 through page 7, line 6 of the instant specification.

Claims 41, 42, 68 and 69 have been amended for clarity.

New claim 99 is drawn to further clarify the eukariotic genomic sequences recited in claims 41 and 68. Support for new claim 99 can be found, for example, on page 7, lines 5-6 of the specification.

Therefore, these amendments do not introduce new matter. Accordingly, entry thereof is respectfully requested.

II. REJECTION UNDER 35 U.S.C. §112, 1ST PARAGRAPH

Claims 31-35, 40-42, 51, 58-62, 67-69, 78, 97 and 98 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement by containing subject matter which was not described in the specification in such a way as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/or use the invention commensurate in scope with these claims. The Examiner alleges that the disclosure does not provide support that the claimed invention was enabled at the time of filing. Careful consideration has been given to the grounds for rejection. Reconsideration is respectfully requested in view of the discussion provided below.

It is respectfully submitted that the enzyme replacement therapy for Fabry disease was known to those skilled in the art at the time the invention was made. Schiffmann with colleagues (Schiffmann *et al.*, "Infusion of α -Galactosidase A Reduces Tissue Globotriaosylceramide Storage In Patients With Fabry Disease," *PNAS USA* 97(1)365-370 (2000)) demonstrated that a single *i/v* infusion of α -Galactosidase A, prepared from transfected human fibroblasts, was well tolerated and significantly reduced GB₃ levels in the liver and shed renal tubular epithelial cells in the urine sediment. In a later work (Schiffmann

et al., Enzyme Replacement Therapy in Fabry Disease: A Randomized Controlled Trial," *JAMA*, 285(21):2743-2749 (2001), which was the first published report of significant clinical benefits from a double-blind placebo-controlled study of the enzyme replacement therapy for Fabry disease conducted on 26 male patients from December 1998 to August 1999 at the Clinical Research Center of the National Institutes of Health, the authors reported a significant reduction of neuropathic pain, improvement in patients' heart and kidney function and decrease in plasma levels of Gb₃.

The results of clinical trials of α -Galactosidase A reported by Eng (Eng *et al.*, "A Phase 1/2 Clinical Trial of Enzyme Replacement Therapy in Fabry Disease: Pharmacokinetic, Substrate Clearance, and Safety Studies," *Am J Hum Genet* 68:711-722 (2001) and Eng *et al.*, "A Multicenter Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Recombinant Human α -Galactosidase A Replacement Therapy in Fabry Disease," *N Engl J Med* 345:9-16 (2001)) demonstrated that the enzyme replacement therapy can prevent further deterioration and in some instances can reverse some of the major pathological consequences of the disease.

Therefore, the enzyme replacement therapy for Fabry disease was well-known and shown effective and safe to those skilled in the art at the time the invention was made.

It is further respectfully submitted that the state of the art at the time the invention was made was that gene transfer therapy for Fabry disease was well-known and appreciated by those skilled in the art. For example, U.S. Patent No. 6,066,626 disclosed recombinant viral and non-viral vectors, comprising a transgene encoding a biologically active human lysosomal enzyme, that were able to infect and transfect and sustain expression of the biologically active human lysosomal enzyme transgene in mammalian (mouse) cells deficient therein.

Jung and colleagues (Jung *et al.*, "Adeno-associated viral vector-mediated gene transfer results in long-term enzymatic and functional correction in multiple organs of Fabry mice," *PNAS USA* 98(5):2676-2681 (2001)) reported construction of a recombinant adeno-associated viral vector encoding human α -galactosidase A (α -gal A) (rAAV-AGA) and its injection into the hepatic portal vein of Fabry mice. Two weeks postinjection, α -gal A activity in the livers of rAAV-AGA-injected Fabry mice was 20-35% of that of the normal mice. The transduced animals continued to show higher α -gal A levels in liver and other tissues compared with the untouched Fabry controls as long as 6 months after treatment. In parallel to the elevated enzyme levels, the authors reported significant reductions in Gb3

levels to near normal at 2 and 5 weeks posttreatment. The lower Gb3 levels continued in liver, spleen, and heart, up to 25 weeks with no significant immune response to the virus or α -gal A. There were no reports of liver toxicity occurred after the rAAV-AGA administration. These findings suggested that an AAV-mediated gene transfer is useful for the treatment of Fabry disease and overall that gene therapy holds a strong potential for treating Fabry disease in humans.

The potential of preselective gene therapy for treatment of Fabry disease was shown by Qin *et al.* (Qin *et al.*, "Preselective Gene Therapy for Fabry Disease," *PNAS USA* 98(6):3428-3433 (2001)). The authors demonstrated the use of bicistronic retroviral vector that engineered expression of the therapeutic α -gal A gene and the human IL-2R α chain (huCD25) gene as selected markers and showed that preselection of transduced Fabry mouse bone marrow cells elevated the level of multilineage gene-corrected hematopoietic cells in the circulation of transplanted animals and improved *in vivo* enzymatic activity levels in plasma and organs for more than 6 months after both primary and secondary transplantation.

The National Institutes of Health, Clinical Center reported the study of gene therapy for Gaucher's and Fabry diseases. The study was conducted from January 1988 and completed in April 2002 and revealed that a retroviral construct, containing human glucocerebrosidase cDNA driven by the MoLV promoter, was highly effective in transferring copies of genes responsible for making lacking enzymes into the cells of patients with Gaucher's or Fabry diseases and positive clinical outcome.

Thus, the common knowledge of using an enzyme replacement therapy and gene transfer therapy for treatment of Fabry disease on animal models and in human trials existed at the time the invention was made. Therefore, based on aforementioned and the original disclosure, it is respectfully submitted that the specification and claims are fully enabling to one of skill in the art to use the method for treatment of a metabolic disorder or condition related to an α -galactosidase A deficiency. It is respectfully requested that the rejection of claims 31-35, 40-42, 51, 58-62, 67-69, 78, 97 and 98 under 35 U.S.C. §112, first paragraph, be withdrawn.

It is believed that Applicant addressed all the issues raised by the Examiner in the Office Action dated April 4, 2006. The issues raised in the Office Action dated June 30, 2005, on which the Examiner did not presently comment, were addressed in the response filed

December 29, 2005, and the arguments considered to be accepted by the Examiner.

III. REJECTION UNDER 35 U.S.C. §112, 2nd PARAGRAPH

Claims 31-35, 40-42, 51, 58-62, 67-69 and 78 remain rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner argues that claims 41, 42, 68 and 69 are indefinite in their recitation of the phrase "comprising...genomic sequences flanking said expression cassette" since the expression cassettes implicitly comprise genomic sequences. Reconsideration is respectfully requested in view of the amendments to the claims.

With respect to alleged indefiniteness of claims 41, 42, 68 and 69, these claims have been amended to define the flanking genomic sequence as homologous to an eukaryotic genomic sequence (claims 41 and 68) and a viral genomic sequence (claims 42 and 69). As amended, these claims distinguish the flanking genomic sequences from polynucleotide sequences of interest comprised by the expression cassette and described as nucleic acid sequences encoding a therapeutic product, such as an enzyme, blood derivative, hormone, cytokine, *etc.* (see, the specification, for example, on page 5, lines 20-30). Thus, as amended claims 41, 42, 68 and 69 are definite. Therefore, it is respectfully requested that the rejection of claims 41, 42, 68 and 69 under 35 U.S.C. §112, second paragraph, be withdrawn.

Claims 31, 58 and their dependent claims remain rejected because the method steps allegedly do not recite any step relating to "treatment". We believe that claims 31 and 58 are complete and, therefore, definite. It is respectfully requested to reconsider the rejection of claims 31, 58 and their dependent claims under 35 U.S.C. §112, second paragraph, and withdraw the rejection of same.

IV. REJECTION UNDER 35 U.S.C. §103(a) OVER GOLDSPINK IN VIEW OF JEANG

Claims 31-35, 40-42 and 51 remain rejected under 35 U.S.C. 103(a) as obvious over Goldspink *et al.*, (WO 94/28151, hereinafter, "Goldspink") in view of Jeang *et al.* (*Molecular and Cellular Biology*, 1984, 4:2214-2223, hereinafter "Jeang"). In particular, the Examiner argues that it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to replace the truncated rabbit β -cardiac myosin heavy chain promoter of Goldspink with the CMV promoter described by Jeang in order to obtain an

expression vector that drives expression of a transgene at high levels. This rejection is traversed. Reconsideration is respectfully requested.

As noted in the response to the previous Office Action, filed December 29, 2005, and admitted by the Examiner (see, Office Action dated June 30, 2005, page 15), Goldspink does not teach the use of a viral promoter.

Jeang teaches that two recombinant plasmids (pTJ148 & pTJ198), containing the DNA fragment from cytomegalovirus (CMV) and transfected into mouse Ltk⁻ cells and LH₂p192-3 cells, provoked constitutive synthesis of the IE-94 (a 94-kilodalton immediate-early protein), which was indistinguishable in size and overall net charge from that produced in virus-infected cells. It was further disclosed that the isolated clonal Ltk⁺ cell line contained two to four stably integrated copies of the IE-94 gene and synthesized a single virus-specific mRNA of 2.5 kilobases. Although the complex and fragmented integration pattern observed in LH₂p192-3 cells precludes an unambiguous determination that the abundant expression of IE94 is driven from an integrated IE94 gene retaining a viral promoter (see, Jeang, page 2222, lines 6-10), it was suggested that the CMV gene together (*emphasis added*) with its promoter and spliced mRNA structure may contain all of the regulatory elements necessary for strong constitutive expression in mammalian cells in the absence of other viral factors. As such, the reference does not teach that the viral (CMV) promoter contains all of the regulatory elements necessary for strong constitutive expression, rather a combination of the CMV gene, promoter and spliced mRNA does. Thus, Jeang does not provide a suggestion or motivation to combine its teachings with those of Goldspink to replace the β-cardiac myosin heavy chain promoter of Goldspink with the CMV promoter to arrive at the expression cassette as instantly claimed. Therefore, claims 31 and claims dependent therefrom, are not obvious over Goldspink in view of Jeang. Accordingly, it is respectfully requested that the rejection of claims 31-35, 40-42 and 51 under 35 U.S.C. 103(a), be withdrawn.

CONCLUSION

In light of the above amendments and remarks, Applicant respectfully submits that claims 31-35, 40-42, 51, 58-62, 67-69, 78 and 97-99 satisfy all the criteria for patentability and requests to consider the subject application towards allowance.

No fees other than the extension of time fees are believed to be due. However, the Commissioner is hereby authorized to charge any required fee(s) to Jones Day Deposit Account No. 50-3013 (referencing the Attorney Docket No. 10103-004-999).

Respectfully submitted,

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